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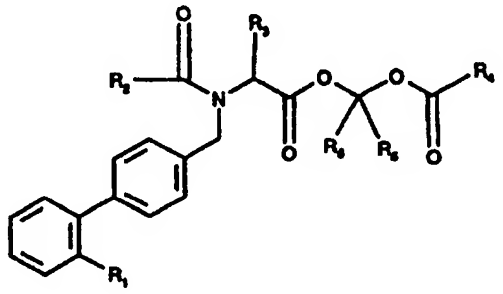
(57) Abstract

The invention relates to a compound of formula (I) or a salt thereof, wherein R_1 is carboxy, lower alkoxycarbonyl or tetrazol-5-yl; R_2 is lower alkyl; R_3 is lower alkyl; R_4 is alkyl, C_3-C_7 cycloalkyl, aryl, alkoxy, C_3-C_7 cycloalkoxy or aryloxy; and R_5 and R_6 are each independently of the other hydrogen or lower alkyl; or R_5 and R_6 together are C_2-C_6 alkylene; to processes for their preparation, to pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and to the use of a compound of formula (I) or of a salt thereof.



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Aryl derivatives

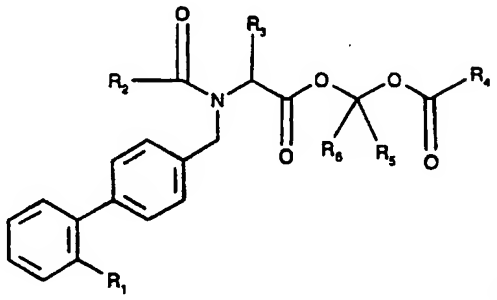
Background to the invention

It is known that angiotensin II has powerful vasoconstrictive properties and, in addition, stimulates aldosterone secretion, thus causing marked sodium/water retention. The consequence of angiotensin II activity manifests itself *inter alia* in a rise in blood pressure. The importance of angiotensin II antagonists is that, by competitive inhibition of the binding of angiotensin II to the receptors, the vasoconstrictive and aldosterone secretion-stimulating effects caused by angiotensin II are suppressed.

The present invention relates to the provision of novel angiotensin II antagonists, to their preparation, to pharmaceutical compositions and to their use.

Description of the invention

The invention relates to a compound of formula (I)



(I)

or a salt thereof, wherein

R_1 is carboxy, lower alkoxycarbonyl or tetrazol-5-yl;

R_2 is lower alkyl;

R_3 is lower alkyl;

R_4 is alkyl, C_3-C_7cycloalkyl, aryl, alkoxy, C_3-C_7cycloalkoxy or aryloxy; and

R_5 and R_6 are each independently of the other hydrogen or lower alkyl; or

R_5 and R_6 together are C_2-C_6alkylene;
to processes for the preparation thereof, to pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and to the use of a compound of formula (I) or of a salt thereof.

The compounds (I) may be in the form of salts, especially pharmaceutically acceptable salts. If the compounds (I) have, for example, at least one basic centre, they can form acid addition salts. Those salts are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, a phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as unsubstituted or substituted, for example halo-substituted, C_1-C_4alkanecarboxylic acids, for example acetic acid, saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, amino acids, for example aspartic or glutamic acid, or benzoic acid, or with organic sulfonic acids, such as unsubstituted or substituted, for example halo-substituted, C_1-C_4alkane- or aryl-sulfonic acids, for example methane- or p-toluene-sulfonic acid. Corresponding acid addition salts can also be formed with a basic centre that may additionally be present. Moreover, compounds (I) having at least one acidic group (for example COOH or 1H-tetrazol-5-yl) can form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethyl-propyl-amine, or a mono-, di- or tri-hydroxy-lower alkylamine, for example mono-, di- or tri-ethanolamine. Corresponding internal salts can also be formed. Also included are salts that are not suitable for pharmaceutical applications, which are used, for example, for the isolation or purification of free compounds (I) or their pharmaceutically acceptable salts.

Tetrazol-5-yl (R_3) is in mesomeric form, especially in the form of the 1H- and 2H-tetrazol-5-yl meso-isomer. Tetrazol-5-yl is predominantly in the form of 2H-tetrazol-5-yl.

Alkyl is, for example, C_1-C_{10}alkyl, preferably lower alkyl.

Aryl is, for example, a carbocyclic or heterocyclic aromatic radical, especially phenyl or naphthyl or, especially, a corresponding 5- or 6-membered monocyclic radical that contains up to four identical or different hetero atoms, such as nitrogen, oxygen or sulfur atoms, preferably one, two, three or four nitrogen atoms, one oxygen atom or one sulfur atom. Corresponding 5-membered heteroaryl radicals are, for example, monoaza-, diaza-, triaza-, tetraaza-, monooxa- or monothia-cyclic aryl radicals, such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl and thienyl, while a suitable corresponding 6-membered radical is especially pyridyl. Corresponding aromatic radicals are unsubstituted or mono- or poly-substituted, for example di- or tri-substituted, for example by identical or different substituents, for example selected from: halogen, trifluoromethyl, hydroxy, lower alkyl, lower alkoxy, hydroxy-lower alkyl and halo-lower alkyl.

Alkoxy is, for example, C_1-C_{10}alkoxy, especially lower alkoxy.

Aryloxy is, for example, phenoxy or naphthyloxy, each of which is unsubstituted or mono- or poly-substituted, for example di- or tri-substituted, by identical or different substituents, for example selected from the group consisting of: halogen, trifluoromethyl, hydroxy, lower alkyl, lower alkoxy, hydroxy-lower alkyl and halo-lower alkyl.

Unless defined otherwise, the general terms used hereinbefore and hereinafter have the meanings indicated below.

The term "lower" means that groups and compounds so designated each contain from 1 up to and including 7 carbon atoms, preferably from 1 up to and including 4 carbon atoms.

Lower alkoxycarbonyl is especially C_2-C_8alkoxycarbonyl and is, for example, methoxy-, ethoxy-, propyloxy- or pivaloyloxy-carbonyl. C_2-C_5alkoxycarbonyl is preferred.

Lower alkyl is, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or a corresponding pentyl, hexyl or heptyl radical. C_1-C_4alkyl is preferred.

C_3-C_7cycloalkyl is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Cyclopentyl and cyclohexyl are preferred.

Naphthyl is 1- or 2-naphthyl.

Lower alkoxy is, for example, methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, iso-butyloxy, sec-butyloxy, tert-butyloxy or a corresponding pentyloxy, hexyloxy or heptyloxy radical. C_1-C_4alkoxy is preferred.

C_3-C_7cycloalkoxy is, for example, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyl-oxy and cycloheptyloxy. Cyclopentyloxy and cyclohexyloxy are preferred.

C_2-C_6alkylene is, for example, ethylene, propylene, butylene, pentylene, hexylene, 2-methyl-propylene or 2,3-dimethyl-butylene.

Pyrrolyl is, for example, 2- or 3-pyrrolyl. Pyrazolyl is 3- or 4-pyrazolyl. Imidazolyl is 2- or 4-imidazolyl. Triazolyl is, for example, 1,3,5-1H-triazol-2-yl or 1,3,4-triazol-2-yl. Tetrazolyl is, for example, 1,2,3,4-tetrazol-5-yl. Furyl is 2- or 3-furyl, and thienyl is 2- or 3-thienyl, while there come into consideration as pyridyl 2-, 3- and 4-pyridyl.

Halogen is especially halogen having an atomic number of up to and including 35, such as fluorine, chlorine or bromine, and also includes iodine.

Hydroxy-lower alkyl is especially hydroxy-C_1-C_4alkyl, such as hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl.

Halo-lower alkyl is especially halo-C_1-C_4alkyl, such as trifluoromethyl, 1,1,2-trifluoro-2-chloro-ethyl or chloromethyl.

Extensive pharmacological investigations have shown that compounds (I) and (IA) and their pharmaceutically acceptable salts have, for example, pronounced angiotensin II-antagonising properties.

The angiotensin II-antagonising properties of the compounds of formulae (I) and (IA) and their pharmaceutically acceptable salts can be determined in the angiotensin II binding test. In that test, smooth muscle cells of rats from homogenised rat aorta are used. The solid

centrifugate is suspended in 50 mM Tris buffer (pH 7.4) using peptidase inhibitors. The samples are incubated for 60 minutes at 25°C with ^{125}I-angiotensin II (0.175 nM) and a varying concentration of angiotensin II or of test compound. Incubation is then terminated by the addition of sodium chloride buffered with ice-cold phosphate, and filtration is carried out through Whatman GF/F filters. The filters are counted using a gamma counter. The IC_{50} values are determined from the dose-effect curve. For the compounds of formulae (I) and (IA) and their pharmaceutically acceptable salts, IC_{50} values are determined from approximately 1 nM.

In order to determine angiotensin II-induced vasoconstriction, tests on isolated rabbit aorta rings can be used. For that purpose, aorta rings are dissected from each thorax and are fixed between two parallel clamps at an initial tension of 2 g. The rings are then immersed at 37°C in 20 ml of a tissue bath and are gassed with a mixture of 95 % O_2 and 5 % CO_2. The isometric reactions are measured. At 20-minute intervals, the rings are stimulated alternately with 10 nM angiotensin II (Hypertensin-CIBA) and 5 nM noradrenaline chloride. The rings are then incubated with selected concentrations of the test compounds before being treated with the agonists. The data are analysed using a Buxco digital computer. The concentrations that effect 50 % inhibition of the initial control values are given as the IC_{50} values. For the compounds of formulae (I) and (IA) and their pharmaceutically acceptable salts, IC_{50} values are determined from approximately 5 nM.

The fact that the compounds of formulae (I) and (IA) and their pharmaceutically acceptable salts are able to lower high blood pressure induced by angiotensin II can be verified using the test model of the normotensive, narcotised rat. After calibration of the preparations with 0.9 % NaCl (1 ml/kg i.v.), noradrenaline (1 µg/kg i.v.) or angiotensin II (0.3 µg/kg i.v.), increasing doses (3-6) of the test compound are injected intravenously by bolus injection, angiotensin II or noradrenaline then being administered at 5-minute intervals after each dose. The blood pressure is measured directly in the carotid artery and is recorded using an on-line data collection system (Buxco). The specificity of the angiotensin II antagonism is shown by the selective inhibition of the pressure effect caused by angiotensin II but not of that caused by noradrenaline. In this test model, the compounds of formulae (I) and (IA) and their pharmaceutically acceptable salts exhibit an inhibitory effect at a dose of approximately 0.3 mg/kg i.v. and above.

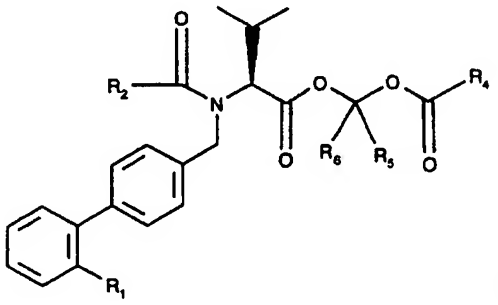
The antihypertensive activity of the compounds of formulae (I) and (IA) and their pharmaceutically acceptable salts can also be demonstrated in the test model of the renal hypertensive rat. In male rats, high blood pressure is brought about by constricting a renal artery by the Goldblatt method. Doses of the test compound are administered to the rats by means of a stomach probe. Control animals receive an equivalent volume of solvent. Blood pressure and heartbeat are measured on conscious animals at intervals indirectly by the tail-clamp method of Gerold *et al.* [Helv. Physiol. Acta 24 (1966), 58] before administration of the test compound or of the solvent and in the course of the experiments. The pronounced antihypertensive effect can be demonstrated at a dose of less than approximately 100 mg/kg p.o..

Accordingly, the compounds of formulae (I) and (IA) and their pharmaceutically acceptable salts can be used, for example, as active ingredients in antihypertensives, which are used, for example, in the treatment of high blood pressure and of congestive heart failure. Accordingly, the invention relates to the use of the compounds of formulae (I) and (IA) and their pharmaceutically acceptable salts in the preparation of corresponding medicaments and in the therapeutic treatment of high blood pressure and of congestive heart failure. The preparation of the medicaments also includes the commercial manufacture of the active substances.

The invention relates especially to a compound of formula (I) or a salt thereof wherein
R_1 is carboxy, lower alkoxycarbonyl or tetrazol-5-yl;
R_2 is lower alkyl, such as C_3-C_5alkyl;
R_3 is lower alkyl, such as 2-propyl;
R_4 is C_1-C_{10}alkyl, C_3-C_7cycloalkyl, phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl, pyridyl, C_1-C_{10}alkoxy, C_3-C_7cycloalkoxy, phenoxy or naphthyloxy; and
R_5 and R_6 are each independently of the other hydrogen or lower alkyl, such as methyl; or
R_5 and R_6 together are C_3-C_6alkylene;
heterocyclic or carbocyclic aromatic radicals being unsubstituted or mono- or poly-substituted by identical or different substituents selected from: halogen, trifluoromethyl, hydroxy, lower alkyl, lower alkoxy, hydroxy-lower alkyl and halo-lower alkyl.

The invention relates more especially to a compound of formula (I) or a salt thereof wherein the carbon atom to which R_3 is bonded is in the (S) form.

The invention relates especially to a compound of formula (IA)



(IA)

or a salt thereof, wherein

R_1 is tetrazol-5-yl;

R_2 is C_3-C_5alkyl, such as n-butyl;

R_4 is lower alkyl, such as methyl or tert-butyl, lower alkoxy, such as isopropyloxy, or C_3-C_6-cycloalkoxy, such as cyclohexyloxy;

R_5 is hydrogen; and

R_6 is hydrogen or lower alkyl, such as methyl.

The invention relates especially to a compound of formula (IA) or a salt thereof wherein

R_1 is tetrazol-5-yl;

R_2 is n-butyl;

R_4 is C_1-C_4alkyl, such as methyl or tert-butyl, C_1-C_4alkoxy, such as isopropyloxy, or C_3-C_6-cycloalkoxy, such as cyclohexyloxy;

R_5 is hydrogen; and

R_6 is hydrogen or C_1-C_4alkyl, such as methyl.

The invention relates especially to a compound of formula (IA) or a salt thereof wherein

R_1 is tetrazol-5-yl;

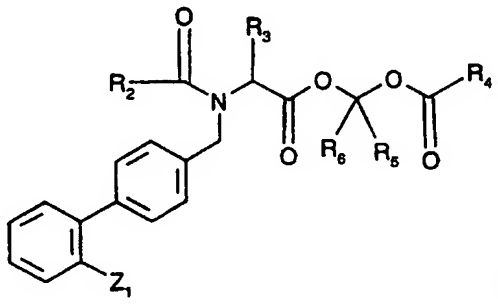
R_2 is C_3-C_5alkyl, especially n-butyl;

R_4 is C_3-C_6cycloalkoxy, such as cyclohexyloxy;
R_5 is hydrogen; and
R_6 is lower alkyl, such as methyl.

The invention relates more especially to the novel compounds mentioned in the Examples and to the methods of preparation described therein.

The invention relates to processes for the preparation of the compounds of the invention. The preparation of compounds of formulae (I) and (IA) and their salts comprises, for example,

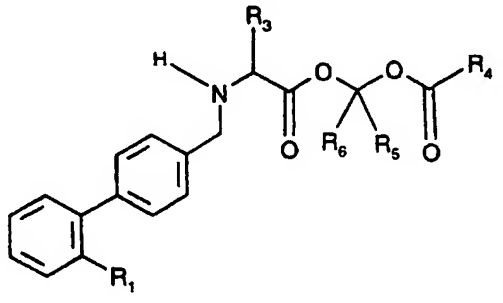
(a) in a compound of formula (II)



(II)

or a salt thereof, wherein Z_1 is a radical that can be converted into R_1, converting Z_1 into R_1; or

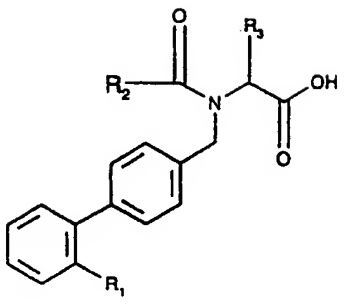
(b) reacting a compound of the formula R_2-COOH (IIIa), a reactive derivative thereof or a salt thereof with a compound of formula (IIIb)



(IIIb)

or a salt thereof; or

(c) reacting a compound of formula (IVa)



(IVa),

a reactive derivative thereof or a salt thereof with a compound of the formula Z_2-C(R_5)(R_6)-OOC-R_4 (IVb), wherein Z_2 is reactive esterified hydroxy, for example in the presence of a base;

and, if desired, converting a compound (I) obtainable according to the process or by other means, in free form or in the form of a salt, into a different compound (I), separating a mixture of isomers obtainable according to the process and isolating the desired isomer, and/or converting a free compound (I) obtainable according to the process into a salt or converting a salt of a compound (I) obtainable according to the process into the free compound (I) or into a different salt.

Radicals Z_1 that can be converted into the variable R_1 are, for example, cyano, as well as functionally modified forms other than COOH and lower alkoxycarbonyl, and also N-protected 5-tetrazolyl.

Reactive derivatives of compounds of formula (IIIa) are, for example, activated esters or reactive anhydrides derived therefrom, and also reactive cyclic amides.

Salts of starting materials that have at least one basic centre, for example of formula (IIIb), are corresponding acid addition salts, while salts of starting materials that have an acidic

group, for example of formula (IIIa), are in the form of salts with bases, in each case as mentioned hereinbefore in connection with corresponding salts of formulae (I) and (IA).

The reactions described hereinbefore and hereinafter in the variants are carried out in a manner known *per se*, for example in the absence or, customarily, in the presence of a suitable solvent or diluent or of a mixture thereof, the reaction being carried out, as required, with cooling, at room temperature or with heating, for example in a temperature range of approximately from -80°C to the boiling temperature of the reaction medium, preferably from approximately -10°C to approximately +200°C, and, if necessary, in a closed vessel, under pressure, under an inert gas atmosphere and/or under anhydrous conditions.

Process variant (a):

Radicals Z_1 that can be converted into tetrazol-5-yl R_1 are, for example, cyano or protected 5-tetrazolyl.

For the preparation of compounds of formulae (I) and (IA) wherein R_1 is tetrazol-5-yl, there is used, for example, a starting material of formula (II) wherein Z_1 is cyano and that starting material is reacted with an azide, such as HN_3, or especially a salt, such as an alkali metal salt, thereof or with an organotin azide, such as a tri-(lower) alkyl- or triaryl-tin azide. Preferred azides are, for example, sodium and potassium azide as well as tri-C_1-C_4alkyl-tin azide, for example trimethyl-, triethyl- or tributyl-tin azide, and triphenyltin azide.

Suitable protecting groups of protected tetrazol-5-yl are the protecting groups customarily employed in tetrazole chemistry, especially triphenylmethyl, unsubstituted or substituted, for example nitro-substituted, benzyl, such as 4-nitrobenzyl, lower alkoxymethyl, such as methoxy- and ethoxy-methyl, lower alkylthiomethyl, such as methylthiomethyl, silyl, such as tri-lower alkylsilyl, for example dimethyl-tert-butyl- and triisopropyl-silyl, and 2-cyanoethyl, and also lower alkoxy-lower alkoxymethyl, such as 2-methoxyethoxymethyl, benzyloxy-methyl and phenacyl.

The protecting groups are removed in accordance with known methods, for example as described in J. Green, Protective Groups in Organic Synthesis, Wiley-Interscience (1980).

For example, the triphenylmethyl group is customarily removed by hydrolysis, especially in the presence of an acid, or by hydrogenolysis in the presence of a hydrogenation catalyst; 4-nitrobenzyl is removed, for example, by hydrogenolysis in the presence of a hydrogenation catalyst; methoxy- or ethoxy-methyl is removed, for example, by treatment with a tri-lower alkyltin bromide, such as triethyl- or tributyl-tin bromide; methylthiomethyl is removed, for example, by treatment with trifluoroacetic acid; silyl radicals are removed, for example, by treatment with fluorides, such as tetra-lower alkylammonium fluorides, for example tetra-butylammonium fluoride, or alkali metal fluorides, for example sodium fluoride; 2-cyanoethyl is removed, for example, by hydrolysis, for example with sodium hydroxide solution; 2-methoxyethoxymethyl is removed, for example, by hydrolysis, for example with hydrochloric acid; and benzyloxymethyl and phenacyl are removed, for example, by hydrogenolysis in the presence of a hydrogenation catalyst.

Compounds of formula (II) are described, for example, in EP 443 983.

A radical Z_1 that can be converted into R_1 = COOH is, for example, functionally modified carboxy, such as cyano, esterified or amidated carboxy, hydroxymethyl or formyl.

Esterified carboxy is, for example, carboxy esterified by an unsubstituted or substituted aliphatic, cycloaliphatic or aromatic alcohol. An aliphatic alcohol is, for example, a lower alkanol, such as methanol, ethanol, propanol, isopropanol, n-butanol, sec-butanol or tert-butanol, while there is suitable as a cycloaliphatic alcohol, for example, a 3- to 8-membered cycloalkanol, such as cyclopentanol, cyclohexanol or cycloheptanol. An aromatic alcohol is, for example, a phenol or a heterocyclic alcohol, each of which may be unsubstituted or substituted, especially hydroxypyridine, for example 2-, 3- or 4-hydroxypyridine. Carboxy may also be esterified by a silylated alcohol and is especially tri(C_1-C_4)alkylsilyl-(C_1-C_4)-alkoxycarbonyl, especially trimethylsilylethoxycarbonyl.

Amidated carboxy is, for example, carbamoyl, carbamoyl monosubstituted by hydroxy, amino or by unsubstituted or substituted phenyl, carbamoyl mono- or di-substituted by lower alkyl, or carbamoyl disubstituted by 4- to 7-membered alkylene or by 3-aza-, 3-lower alkyl-aza-, 3-oxo- or 3-thia-alkylene. There may be mentioned as examples carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, such as N-methyl-, N-ethyl-, N,N-dimethyl-, N,N-diethyl- or N,N-dipropyl-carbamoyl, pyrrolidino- or piperidino-carbonyl, morpholino-, piperazino- or 4-

methylpiperazino- and thiomorpholino-carbonyl, anilinocarbonyl, or anilinocarbonyl substituted by lower alkyl, lower alkoxy and/or by halogen.

Preferred functionally modified carboxy is, for example, lower alkoxycarbonyl, such as methoxy- or ethoxy-carbonyl, tri(C_1-C_4)alkylsilyl-(C_1-C_4)alkoxycarbonyl, especially trimethylsilylethoxycarbonyl, or cyano. Compounds of formulae (I) and (IA) wherein R_1 is carboxy can be prepared, for example, starting from compounds of formula (II) wherein Z_1 is functionally modified carboxy, in a manner known *per se*, for example by hydrolysis, especially in the presence of a base, in the case of corresponding tri(C_1-C_4)alkylsilyl-(C_1-C_4)alkoxycarbonyl derivatives, for example, by treatment with an ammonium fluoride, such as tetra-lower alkylammonium fluoride, for example tetra-n-butylammonium fluoride, or in the case of benzyloxycarbonyl derivatives by hydrogenolysis in the presence of a hydrogenation catalyst, or, starting from compounds of formula (II) wherein Z_1 is hydroxymethyl or formyl, by oxidation using customary oxidising agents.

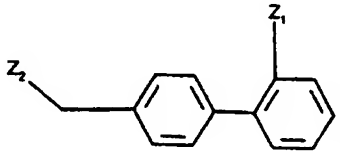
The oxidation is carried out, for example, in an inert solvent, such as a lower alkanecarboxylic acid, for example acetic acid, a ketone, for example acetone, an ether, for example tetrahydrofuran, a heterocyclic aromatic compound, for example pyridine, or water, or in a mixture thereof, if necessary with cooling or heating, for example at from approximately 0°C to approximately 150°C. Suitable oxidising agents are, for example, oxidising transition metal compounds, especially those with elements of sub-group I, VI or VIII. There may be mentioned as examples: silver compounds, such as silver nitrate, oxide or picolinate, chromium compounds, such as chromium trioxide or potassium dichromate, and manganese compounds, such as potassium permanganate, tetrabutylammonium permanganate or benzyl(triethyl)ammonium permanganate. Other oxidising agents are, for example, suitable compounds with elements of the 4th main group, such as lead dioxide, or halogen-oxygen compounds, such as sodium iodate or potassium periodate.

For example, hydroxymethyl and formyl are oxidised to carboxy R_1.

Suitable bases are, for example, alkali metal hydroxides, hydrides, amides, alkanolates, carbonates, triphenylmethylides, di-lower alkylamides, aminoalkylamides or lower alkylsilylamides, naphthaleneamines, lower alkylamines, basic heterocycles, ammonium hydroxides

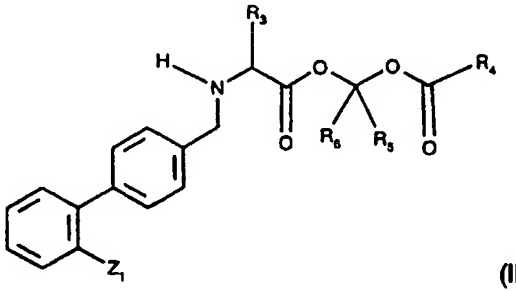
and carbocyclic amines. There may be mentioned by way of example sodium hydroxide, sodium hydride, sodium amide, sodium methoxide, sodium ethoxide, potassium tert-butoxide, potassium carbonate, lithium triphenylmethylide, lithium diisopropylamide, potassium 3-(aminopropyl)amide, potassium bis(trimethylsilyl)amide, dimethylamino-naphthalene, di- or tri-ethylamine, or ethyl-diisopropylamine, N-methyl-piperidine, pyridine, benzyltrimethylammonium hydroxide, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

The starting material of formula (II) is obtainable, for example, by reacting a compound of the formula R_4-COO-C(R_5)(R_6)-OOC-CH(R_3)-NH_2 (IIa) with a compound of the formula



(IIb),

wherein Z_2 is reactive esterified hydroxy, for example in the presence of a base, and, in the next reaction step, reacting the resulting compound of the formula



(IIc)

with a compound of formula (IIIa), for example analogously to variant b).

Reactive esterified hydroxy Z_2 is especially hydroxy esterified by a strong inorganic acid or organic sulfonic acid, for example halogen, such as chlorine, bromine or iodine, sulfonyloxy, such as hydroxysulfonyloxy, halosulfonyloxy, for example fluorosulfonyloxy, unsubstituted or substituted, for example halo-substituted, C_1-C_7alkanesulfonyloxy, for example methane- or trifluoromethane-sulfonyloxy, C_5-C_7cycloalkanesulfonyloxy, for example cyclohexane-

sulfonyloxy, or unsubstituted or substituted, for example C_1-C_7alkyl- or halo-substituted, benzenesulfonyloxy, for example p-bromobenzene- or p-toluene-sulfonyloxy.

Compounds of formula (IIb) are known, for example, from EP 253 310 or can be prepared in a manner known *per se*. Compounds of formula (IIa) are largely known, or they can be obtained analogously to preparation processes known *per se*.

Process variant (b):

Activated esters of compounds of formula (IIIa) are especially esters that are unsaturated at the linking carbon atom of the esterifying radical, for example esters of the vinyl ester type, such as vinyl esters (obtainable, for example, by transesterification of a corresponding ester by vinyl acetate; activated vinyl ester method), carbamoylvinyl esters (obtainable, for example, by treatment of the corresponding acid with an isoxazolium reagent; 1,2-oxazolium or Woodward method) or 1-lower alkoxyvinyl esters (obtainable, for example, by treatment of the corresponding acid with a lower alkoxyacetylene; ethoxyacetylene method), or esters of the amidino type, such as N,N'-disubstituted amidino esters (obtainable, for example, by treatment of the corresponding acid with a suitable N,N'-disubstituted carbodiimide, for example N,N'-dicyclohexylcarbodiimide; carbodiimide method) or N,N-disubstituted amidino esters (obtainable, for example, by treatment of the corresponding acid with an N,N-disubstituted cyanamide; cyanamide method), suitable aryl esters, especially phenyl esters substituted by electron-attracting substituents (obtainable, for example, by treatment of the corresponding acid with a suitably substituted phenol, for example 4-nitrophenol, 4-methylsulfonylphenol, 2,4,5-trichlorophenol, 2,3,4,5,6-pentachlorophenol or 4-phenyldiazophenol, in the presence of a condensing agent, such as N,N'-dicyclohexylcarbodiimide; activated aryl ester method), cyanomethyl esters (obtainable, for example, by treatment of the corresponding acid with chloroacetonitrile in the presence of a base; cyanomethyl ester method), thio esters, especially unsubstituted or substituted, for example nitro-substituted, phenylthio esters (obtainable, for example, by treatment of the corresponding acid with unsubstituted or substituted, for example nitro-substituted, thiophenols, *inter alia* by means of the anhydride or carbodiimide method; activated thiol ester method) or, especially, amino or amido esters (obtainable, for example, by treatment of the corresponding acid with an N-hydroxyamino or N-hydroxyamido compound and their activated derivatives, for example N-hydroxysuccinimide, N-hydroxypiperidine, N-hydroxyphthalimide, N-hydroxy-5-norbornene- or N-hydroxy-5-norbornane-2,3-dicarboxylic acid imide, 1-

hydroxybenzotriazole or benzotriazol-1-yloxyphosphonium salts or benzotriazol-1-yluronium salts, or 3-hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-one, for example by the anhydride or carbodiimide method; activated N-hydroxy ester method).

Anhydrides of acids can be symmetrical or, preferably, mixed anhydrides of those acids, for example anhydrides with inorganic acids, such as acid halides, especially acid chlorides (obtainable, for example, by treatment of the corresponding acid with thionyl chloride, phosphorus pentachloride or oxalyl chloride; acid chloride method), azides (obtainable, for example, from a corresponding acid ester *via* the corresponding hydrazide and treatment thereof with nitrous acid; azide method), anhydrides with carbonic acid semiesters, for example carbonic acid lower alkyl semiesters (obtainable, for example, by treatment of the corresponding acid with chloroformic acid lower alkyl esters or with a 1-lower alkoxycarbonyl-2-lower alkoxy-1,2-dihydroquinoline, for example 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline; mixed O-alkylcarbonic anhydride method), anhydrides with dihalogenated, especially dichlorinated, phosphoric acid (obtainable, for example, by treatment of the corresponding acid with phosphorus oxychloride; phosphorus oxychloride method), anhydrides with other phosphoric acid derivatives (for example those that can be obtained with phenyl N-phenylphosphoramidochloridate) or with phosphorous acid derivatives, or anhydrides with organic acids, such as mixed anhydrides with organic carboxylic acids (obtainable, for example, by treatment of the corresponding acid with an unsubstituted or substituted lower alkane- or phenyl-lower alkane-carboxylic acid halide, for example phenylacetic acid chloride, pivalic acid chloride or trifluoroacetic acid chloride; mixed carboxylic anhydride method) or with organic sulfonic acids (obtainable, for example, by treatment of a salt, such as an alkali metal salt, of the corresponding acid with a suitable organic sulfonic acid halide, such as lower alkane- or aryl-, for example methane- or p-toluene-sulfonic acid chloride; mixed sulfonic anhydride method), as well as symmetrical anhydrides (obtainable, for example, by condensation of the corresponding acid in the presence of a carbodiimide or of 1-diethylaminopropyne; symmetrical anhydride method).

Suitable cyclic amides are especially amides with 5-membered diazacycles of aromatic character, such as amides with imidazoles, for example imidazole (obtainable, for example, by treatment of the corresponding acid with N,N'-carbonyldiimidazole; imidazole method), or pyrazoles, for example 3,5-dimethylpyrazole (obtainable, for example, *via* the acid hydrazide by treatment with acetylacetone; pyrazolide method).

The condensation to produce the amide bond can be carried out in a manner known *per se*, for example as described in standard works, such as "Houben-Weyl, Methoden der organischen Chemie", 4th edition, Vol. 15/II, Georg Thieme Verlag, Stuttgart 1974, "The Peptides" (eds. E. Gross and J. Meienhofer), Vol. 1 and 2, Academic Press, London and New York, 1979/1980, or M. Bodanszky, "Principles of Peptide Synthesis", Springer-Verlag, Berlin 1984.

The condensation can be carried out in the presence of one of the customary condensing agents. Customary condensing agents are, for example, carbodiimides, for example diethyl-, dipropyl-, N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide or, especially, dicyclohexylcarbodiimide, also suitable carbonyl compounds, for example carbonyldiimidazole, 1,2-oxazolium compounds, for example 2-ethyl-5-phenyl-1,2-oxazolium 3'-sulfonate and 2-tert-butyl-5-methylisoxazolium perchlorate, or a suitable acylamino compound, for example 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, also activated phosphoric acid derivatives, for example diphenylphosphorylazide, diethylphosphoryl cyanide, phenyl N-phenylphosphoramidochloridate, bis(2-oxo-3-oxazolidinyl)phosphinic acid chloride or 1-benzotriazolyloxy-tris(dimethylamino)phosphonium hexafluorophosphate.

If desired, an organic base is added, for example a tri-lower alkylamine having bulky radicals, for example ethyldiisopropylamine, or a heterocyclic base, for example pyridine, 4-dimethylaminopyridine or, preferably, N-methylmorpholine.

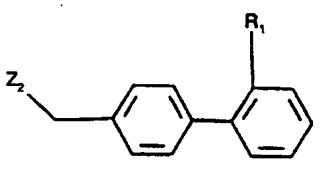
The condensation of acid anhydrides with amines can be carried out, for example, in the presence of inorganic carbonates, for example alkali metal carbonates or hydrogen carbonates, such as sodium or potassium carbonate or hydrogen carbonate (customarily together with a sulfate).

The condensation is preferably carried out in an inert, polar, aprotic, preferably anhydrous, solvent or solvent mixture, for example in a carboxylic acid amide, for example formamide or dimethylformamide, a halogenated hydrocarbon, for example methylene chloride, carbon tetrachloride or chlorobenzene, a ketone, for example acetone, a cyclic ether, for example tetrahydrofuran, an ester, for example ethyl acetate, or a nitrile, for example acetonitrile, or in mixtures thereof, where appropriate at reduced or elevated temperature, for example in a

temperature range of from approximately -40°C to approximately +100°C, preferably from approximately -10°C to approximately +50°C, and, where appropriate, under an inert gas atmosphere, for example a nitrogen atmosphere.

Reactive acid derivatives can also be formed *in situ*.

The starting material of formula (IIIb) can be prepared, for example, by reacting a compound of formula (IIa) with a compound of the formula



(IIIc),

wherein Z_2 is reactive esterified hydroxy, especially in the presence of one of the bases mentioned hereinbefore.

Reactive esterified hydroxy Z_2 is especially hydroxy esterified by a strong inorganic acid or organic sulfonic acid, for example halogen, such as chlorine, bromine or iodine, sulfonyloxy, such as hydroxysulfonyloxy, halosulfonyloxy, for example fluorosulfonyloxy, unsubstituted or substituted, for example halo-substituted, C_1-C_7alkanesulfonyloxy, for example methane- or trifluoromethane-sulfonyloxy, C_5-C_7cycloalkanesulfonyloxy, for example cyclohexane-sulfonyloxy, or unsubstituted or substituted, for example C_1-C_7alkyl- or halo-substituted, benzenesulfonyloxy, for example p-bromobenzene- or p-toluene-sulfonyloxy.

Process variant (c):

The reaction is advantageously carried out in the presence of one of the bases mentioned hereinbefore.

The starting material of formula (IVa) is known, for example, from the European Patent Application having the publication number 443 983 (EP 443 983). The starting material of formula (IVb) is known or can be prepared in a manner known *per se*.

The preparation of compounds of formulae (I) and (IA) can be taken, for example, from the working examples.

A compound of the invention obtainable according to the process can be converted in a manner known *per se* into a different compound of the invention.

The invention relates especially to the processes described in the Examples.

Salts of compounds of formulae (I) and (IA) can be prepared in a manner known *per se*. For example, acid addition salts of compounds of formulae (I) and (IA) are obtained by treatment with an acid or a suitable ion exchange reagent. Salts can be converted into the free compounds in customary manner, acid addition salts, for example, by treatment with a suitable basic agent.

Depending on the procedure and the reaction conditions, the compounds of the invention having salt-forming, especially basic, properties can be obtained in free form or, preferably, in the form of salts.

In view of the close relationship between the novel compounds in free form and in the form of their salts, hereinbefore and hereinafter any reference to the free compounds or their salts is to be understood as including the corresponding salts or the free compounds, respectively, as appropriate and expedient.

The novel compounds, including the salts of salt-forming compounds, can also be obtained in the form of their hydrates or can include other solvents used for crystallisation.

Depending on the starting materials and procedures chosen, the novel compounds can be in the form of one of the possible isomers or in the form of mixtures thereof, for example, depending on the number of asymmetric carbon atoms, in the form of pure optical isomers, such as antipodes, or in the form of mixtures of isomers, such as racemates, mixtures of diastereoisomers or mixtures of racemates. For example, the carbon atom in compounds of formula (I) to which the radical R_3 is bonded is an asymmetric carbon atom. In corresponding compounds of formula (I) wherein one of the radicals R_5 and R_6 is hydrogen and the other is other than hydrogen, a further asymmetric carbon atom is present.

Resulting racemates and mixtures of diastereoisomers can be separated into the pure isomers or racemates on the basis of the physicochemical differences between the constituents in known manner, for example by fractional crystallisation. Resulting racemates can also be resolved into the optical antipodes by known methods, for example by recrystallisation from an optically active solvent, chromatography on chiral adsorbents, with the aid of suitable microorganisms, by cleavage with specific, immobilised enzymes, by way of the formation of inclusion compounds, for example using chiral crown ethers, only one enantiomer being complexed, or by conversion into diastereoisomeric salts, for example by reaction of a basic end product racemate with an optically active acid, such as a carboxylic acid, for example tartaric or malic acid, or a sulfonic acid, for example camphorsulfonic acid, and separation of the resulting mixture of diastereoisomers, for example on the basis of their different solubilities, into the diastereoisomers, from which the desired enantiomer can be freed by the action of suitable agents.

The invention relates also to those forms of the process according to which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining steps are carried out, or a starting material is used in the form of a derivative or salt and/or its racemates or antipodes or, especially, is formed under the reaction conditions.

In the process of the present invention it is preferable to use those starting materials which result in the compounds described at the beginning as being especially valuable. The invention relates also to novel starting materials, which have been developed specifically for the preparation of the compounds of the invention, to their use and to processes for their preparation, the variables R_1, R_2, R_3, R_4, R_5 and R_6 being as defined for the groups of compounds of formulae (I) and (IA) that are preferred in each case. Preferred starting materials are especially compounds of formula (IIa), their tautomers and salts, wherein Z_1 is cyano.

The invention relates also to the use of the compounds of formulae (I) and (IA), or of pharmaceutically acceptable salts of such compounds having salt-forming properties, especially as pharmacological, especially angiotensin II antagonising, active ingredients. They can be used, preferably in the form of pharmaceutically acceptable compositions, in a

method for the prophylactic and/or therapeutic treatment of the animal or human body, especially as angiotensin II antagonists.

The invention relates also to pharmaceutical compositions comprising the compounds of the invention or pharmaceutically acceptable salts thereof as active ingredients, and to processes for their preparation.

The pharmaceutical compositions according to the invention that comprise the compound of the invention or pharmaceutically acceptable salts thereof are compositions for enteral, such as oral, also rectal, and parenteral administration to (a) warm-blooded animal(s), the pharmacological active ingredient being present on its own or together with a pharmaceutically acceptable carrier. The daily dose of active ingredient depends on the age and individual condition and on the mode of administration.

The novel pharmaceutical compositions comprise, for example, from approximately 10 % to approximately 100 %, up to especially 80 %, preferably from approximately 20 % to approximately 60 %, active ingredient. Pharmaceutical compositions according to the invention for enteral or parenteral administration are, for example, compositions in unit dose form, such as dragées, tablets, capsules or suppositories, and also ampoules. These are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, granulating a resulting mixture, where appropriate, and processing the mixture or granules, if desired or necessary, after the addition of suitable excipients to form tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, also binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, if desired disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or

calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable, optionally enteric, coatings, there being used *inter alia* concentrated sugar solutions which may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colourings or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Other pharmaceutical compositions for oral administration are dry-filled capsules consisting of gelatin, and soft sealed capsules consisting of gelatin and a plasticiser, such as glycerine or sorbitol. The dry-filled capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and, where appropriate, stabilisers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it likewise being possible to add stabilisers.

Suitable rectally administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. There may also be used gelatin rectal capsules, which comprise a combination of the active ingredient with a base material. Suitable base materials are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

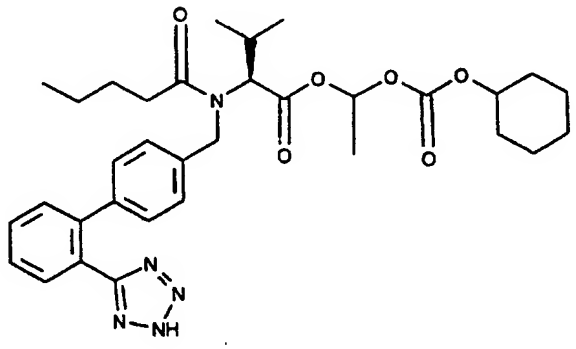
For parenteral administration there are suitable, especially, aqueous solutions of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, also suspensions of the active ingredient, such as corresponding oily injection suspensions, there being used suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, or aqueous injection suspensions that comprise viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran and, if desired, stabilisers.

The dosage of active ingredient depends on the species of warm-blooded animal, the age and individual condition, and the mode of administration. In normal cases, the approximate daily dose for a patient weighing about 75 kg is estimated to be, in the case of oral administration, from approximately 10 mg to approximately 250 mg.

The Examples which follow illustrate the invention described above; however, they are not intended to limit its scope in any way. Temperatures are given in degrees Celsius.

Example 1: (S)-3-Methyl-2-{pentanoyl-[2'-(2*H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid 1-cyclohexyloxycarbonyloxy-ethyl ester

10 g of (S)-3-methyl-2-{pentanoyl-[2'-(2-trityl-2*H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid, 3.7 g of 1-chloroethyl-cyclohexyl carbonate (EP 128 029), 2.4 g of potassium carbonate and 1.2 g of potassium iodide are heated at 60°C for 4 hours, with stirring, in 50 ml of dimethylformamide. Ethyl acetate is added, the mixture is washed three times with water and is dried over sodium sulfate, and concentration by evaporation is carried out *in vacuo*. The residue is taken up in a mixture of 100 ml of methanol and 20 ml of methylene chloride. 22 ml of 1N hydrochloric acid and 20 ml of tetrahydrofuran are added, and stirring is carried out for 2 hours at room temperature. The reaction mixture is concentrated, diluted with water and extracted twice with ethyl acetate, and the organic phase is washed with water and brine, dried and concentrated. The crude product is separated by means of flash chromatography: 260 g of silica gel 60 (40-63 μm), eluant: methylene chloride/methanol 97:3. After concentration of the corresponding fractions by evaporation, (S)-3-methyl-2-{pentanoyl-[2'-(2*H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid 1-cyclohexyloxy-carbonyloxy-ethyl ester is obtained in the form of a white amorphous powder. FAB-MS $(M+H)^+$ 606. Rf value 0.57 (eluant: methylene chloride/methanol/conc. ammonia).



The starting material can be prepared, for example, as follows:

20 g of (S)-3-methyl-2-{pentanoyl-[2'-(2*H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid (EP 443 983) and 7 ml of triethylamine are introduced into 200 ml of methylene chloride, and 13 g of trityl chloride are added in an ice-bath. The mixture is stirred for one hour in the ice-bath, a further 0.1 equivalent of trityl chloride and triethylamine is added, and

stirring is carried out at room temperature for one hour. The reaction mixture is washed twice with water, the aqueous phase is then extracted with methylene chloride, the organic phases are combined and the solvent is removed *in vacuo*. The residue is taken up in a 1:1 mixture of ethyl acetate/hexane and is then washed with sodium carbonate solution, water, 2N hydrochloric acid and again with sodium carbonate. After drying (sodium sulfate), concentration is carried out *in vacuo*. (S)-3-Methyl-2-{pentanoyl-[2'-(2-trityl-*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid is obtained in the form of a white foam. Rf value 0.5 (eluant: methylene chloride/methanol 95:5). The crude product is processed further without being purified.

Example 2:

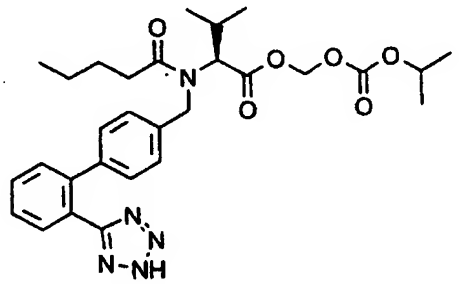
In an analogous manner, the following, for example, can be prepared:

(S)-3-methyl-2-{pentanoyl-[2'-(*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid isopropyloxycarbonyloxy-methyl ester;

(S)-3-methyl-2-{pentanoyl-[2'-(*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid tert-butylcarbonyloxy-methyl ester;

(S)-3-methyl-2-{pentanoyl-[2'-(*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid 1-methylcarbonyloxy-ethyl ester.

Example 3: (S)-3-Methyl-2-{pentanoyl-[2'-(*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid isopropyloxycarbonyloxy-methyl ester



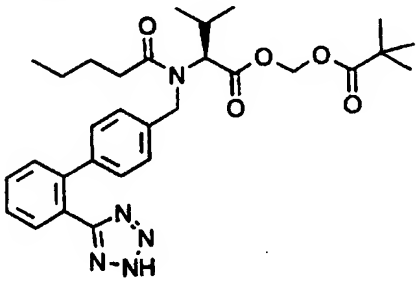
6 ml of 4N aqueous hydrochloric acid are added to 6.3 g of (S)-3-methyl-2-{pentanoyl-[2'-(2-trityl-*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid isopropyloxycarbonyloxy-methyl ester in 50 ml of dimethylformamide. Stirring is carried out at room temperature for 10 hours. The reaction mixture is concentrated a little by evaporation, the residue is taken up in ether and washed twice with water and once with brine, and the organic phase is dried

over sodium sulfate and concentrated by evaporation. The colourless resin is separated by flash chromatography (350 g of silica gel 60 (40-63 μm), eluant: methylene chloride/-methanol 96:4). Lyophilisation from tert-butanol yields the amorphous product (S)-3-methyl-2-{pentanoyl-[2'-(*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid isopropyloxy-carbonyloxy-methyl ester. Rf value 0.5 (eluant: methylene chloride/methanol 9:1). FAB-MS $(M+H)^+$ 552.

The starting material can be obtained, for example, as follows:

1.62 g of chloromethyl-isopropyl carbonate (Chemical Abstracts registration number: 35180-01-9; Synth. Commun. (1990), 20(18), 2865-2885; Synthesis (1971), (11), 588-590) are added to 6 g of (S)-3-methyl-2-{pentanoyl-[2'-(2-trityl-*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid, and the mixture is dissolved in 25 ml of dimethylformamide. 1.47 g of potassium carbonate are added and stirring is carried out at 60°C for 4 hours. The reaction mixture is taken up in ether, extracted with water and brine, dried and concentrated by evaporation. The resinous crude product (S)-3-methyl-2-{pentanoyl-[2'-(2-trityl-*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid isopropyloxycarbonyloxy-methyl ester is used in the next step without being purified further. Rf value 0.96 (eluant: methylene chloride/methanol 9:1).

Example 4: (S)-3-Methyl-2-{pentanoyl-[2'-(*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid pivaloyloxy-methyl ester



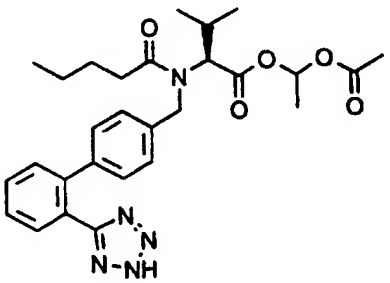
5.4 ml of 4N aqueous hydrochloric acid are added to 5.66 g of (S)-3-methyl-2-{pentanoyl-[2'-(2-trityl-*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid pivaloyloxy-methyl ester in 50 ml of tetrahydrofuran, and stirring is carried out for 10 hours at room temperature. The reaction mixture is concentrated a little by evaporation, the residue is taken up in

ether and washed with water and brine, and the organic phase is dried and concentrated by evaporation. The resulting oil is separated by means of flash chromatography (350 g of silica gel 60 (40-63 µm), eluant: methylene chloride/methanol 96:4). Trituration in n-pentane yields the amorphous product (S)-3-methyl-2-{pentanoyl-[2'-(*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid pivaloyloxy-methyl ester. Rf value 0.48 (eluant: methylene chloride/methanol 9:1). FAB-MS $(M+H)^+$ 550.

The starting material can be obtained, for example, as follows:

1.6 g of pivalic acid chloromethyl ester are added to 6 g of (S)-3-methyl-2-{pentanoyl-[2'-(2-trityl-*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid, and the mixture is dissolved in 25 ml of dimethylformamide. 1.47 g of potassium carbonate are added, followed by 0.735 g of potassium iodide, and stirring is carried out at 60°C for 4 hours. The reaction mixture is taken up in ether, extracted with water and brine, dried and concentrated by evaporation. The resinous crude product (S)-3-methyl-2-{pentanoyl-[2'-(2-trityl-*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid pivaloyloxy-methyl ester is used in the next step without being purified further. Rf value 0.83 (eluant: methylene chloride/methanol 95:5).

Example 5: (S)-3-Methyl-2-{pentanoyl-[2'-(*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid 1-acetoxy-ethyl ester



38 ml of 4N aqueous hydrochloric acid are added to 39 g of (S)-3-methyl-2-{pentanoyl-[2'-(2-trityl-*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid 1-acetoxy-ethyl ester, dissolved in 200 ml of tetrahydrofuran, and stirring is carried out for 10 hours at room temperature. The reaction mixture is concentrated a little by evaporation, the residue is taken up in ether and washed with water and brine, and the organic phase is dried over

sodium sulfate. The crude product is separated by flash chromatography (1 kg of silica gel 60 (40-63 μm), eluant: methylene chloride/methanol 95:5). Trituration in n-pentane yields the amorphous product (S)-3-methyl-2-{pentanoyl-[2'-(*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid 1-acetoxy-ethyl ester. Rf value 0.22 (eluant: methylene chloride/methanol 95:5). FAB-MS $(M+H)^+$ 522.

The starting material can be obtained, for example, as follows:

26.16 g of (S)-3-methyl-2-{pentanoyl-[2'-(2-trityl-*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid are dissolved in 80 ml of dimethylformamide. 6.4 g of potassium carbonate are added, stirring is carried out for 30 minutes, and then 5.68 g of acetic acid 1-chloroethyl ester (Acta Chem. Scand. (1989), 43(1), 74-77) are added. The mixture is heated for 3 hours at 75°C, cooled, taken up in ether, extracted with water and brine, dried and concentrated by evaporation. The resinous crude product (S)-3-methyl-2-{pentanoyl-[2'-(2-trityl-*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid 1-acetoxy-ethyl ester is used in the next step without being purified further. Rf value 0.5 (eluant: hexane/ethyl acetate 2:1).

Example 6: Tablets each comprising 50 mg of active ingredient, for example (S)-3-methyl-2-{pentanoyl-[2'-(*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid 1-cyclohexyloxy-carbonyloxy-ethyl ester, can be prepared as follows:

Composition (for 10 000 tablets):

active ingredient	500.0 g
lactose	500.0 g
potato starch	352.0 g
gelatin	8.0 g
talc	60.0 g
magnesium stearate	10.0 g
silica (highly dispersed)	20.0 g
ethanol	q.s.

The active ingredient is mixed with the lactose and 292 g of potato starch, and the mixture is moistened with an alcoholic solution of the gelatin and granulated through a sieve. After drying, the remaining potato starch, the talc, the magnesium stearate and the highly dispersed silica are mixed in and the mixture is compressed to form tablets which each weigh 145.0 mg and comprise 50.0 mg of active ingredient, and which may, if desired, be provided with dividing notches for finer adaptation of the dose.

Example 7: Film-coated tablets each comprising 100 mg of active ingredient, for example (S)-3-methyl-2-{pentanoyl-[2'-(*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid 1-cyclohexyloxycarbonyloxy-ethyl ester, can be prepared as follows:

Composition (for 1000 tablets):

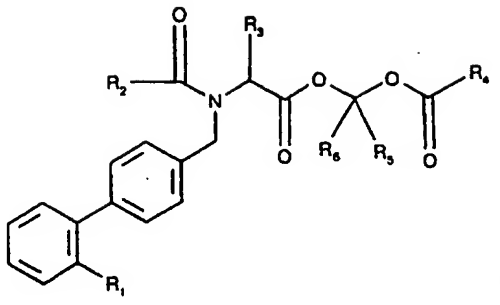
active ingredient	100.00 g
lactose	100.00 g
corn starch	70.00 g
talc	8.50 g
calcium stearate	1.50 g
hydroxypropylmethylcellulose	2.36 g
shellac	0.64 g
water	q.s.
dichloromethane	q.s.

The active ingredient, the lactose and 40 g of corn starch are mixed, and the mixture is moistened with a paste, prepared from 15 g of corn starch and water (with heating), and granulated. The granules are dried, and the remaining corn starch, the talc and the calcium stearate are added and mixed with the granules. The mixture is compressed to form tablets (weight: 280 mg), which are coated with a solution of the hydroxypropylmethylcellulose and the shellac in dichloromethane (final weight of the film-coated tablet: 283 mg).

Example 8: In a manner analogous to that described in Examples 6 and 7 it is also possible to prepare tablets and film-coated tablets comprising a different compound of formula (I) or (IA) or a pharmaceutically acceptable salt of a compound of formula (I) or (IA), for example according to Example 2.

What is claimed is:

1. A compound of formula (I)



(I)

or a salt thereof, wherein

R_1 is carboxy, lower alkoxycarbonyl or tetrazol-5-yl;

R_2 is lower alkyl;

R_3 is lower alkyl;

R_4 is alkyl, C_3-C_7cycloalkyl, aryl, alkoxy, C_3-C_7cycloalkoxy or aryloxy; and

R_5 and R_6 are each independently of the other hydrogen or lower alkyl; or

R_5 and R_6 together are C_2-C_6alkylene.

2. A compound according to claim 1 of formula (I) or a salt thereof, wherein

R_1 is carboxy, lower alkoxycarbonyl or tetrazol-5-yl;

R_2 is lower alkyl;

R_3 is lower alkyl;

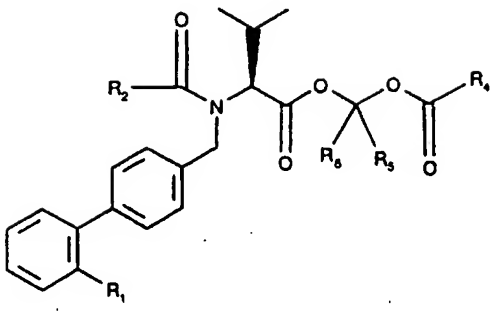
R_4 is C_1-C_{10}alkyl, C_3-C_7cycloalkyl, phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl, pyridyl, C_1-C_{10}alkoxy, C_3-C_7cycloalkoxy, phenoxy or naphthyloxy; and

R_5 and R_6 are each independently of the other hydrogen or lower alkyl; or

R_5 and R_6 together are C_2-C_6alkylene;

heterocyclic or carbocyclic aromatic radicals being unsubstituted or mono- or poly-substituted by identical or different substituents selected from: halogen, trifluoromethyl, hydroxy, lower alkyl, lower alkoxy, hydroxy-lower alkyl and halo-lower alkyl.

3. A compound according to claim 1 of formula (IA)



(IA)

or a salt thereof, wherein

R_1 is tetrazol-5-yl;

R_2 is C_3-C_5alkyl;

R_4 is lower alkyl, lower alkoxy or C_3-C_6cycloalkoxy;

R_5 is hydrogen; and

R_6 is hydrogen or lower alkyl.

4. A compound according to claim 3 of formula (IA) or a salt thereof, wherein

R_1 is tetrazol-5-yl;

R_2 is n-butyl;

R_4 is C_1-C_4alkyl, C_1-C_4alkoxy or C_3-C_6cycloalkoxy;

R_5 is hydrogen; and

R_6 is hydrogen or C_1-C_4alkyl.

5. A compound according to claim 3 of formula (IA) or a salt thereof, wherein

R_1 is tetrazol-5-yl;

R_2 is C_3-C_5alkyl;

R_4 is C_3-C_6cycloalkoxy;

R_5 is hydrogen; and

R_6 is lower alkyl.

6. A compound according to claim 1 selected from:

(S)-3-methyl-2-{pentanoyl-[2'-(*2H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid 1-cyclohexyloxycarbonyloxy-ethyl ester;

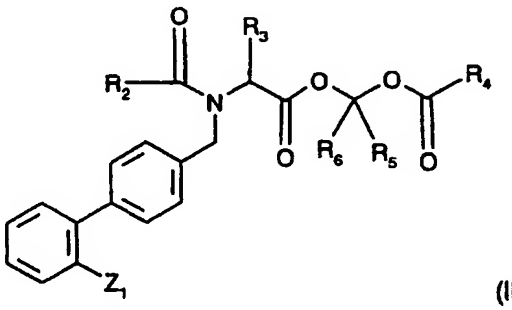
(S)-3-methyl-2-{pentanoyl-[2'-(2*H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid isopropyloxycarbonyloxy-methyl ester;
(S)-3-methyl-2-{pentanoyl-[2'-(2*H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid tert-butylcarbonyloxy-methyl ester; and
(S)-3-methyl-2-{pentanoyl-[2'-(2*H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid 1-methylcarbonyloxy-ethyl ester;
or in each case a salt thereof.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof, where appropriate with the admixture of excipients or adjuvants.

8. The use of a compound according to any one of claims 1 to 6 or of a pharmaceutically acceptable salt thereof in the preparation of a pharmaceutical composition for the treatment of high blood pressure or congestive heart failure.

9. A process for the preparation of a compound according to any one of claims 1 to 6 or of a salt thereof, which comprises

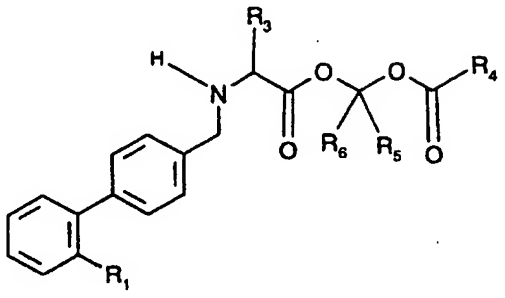
(a) in a compound of formula (II)



(II)

or a salt thereof, wherein Z_1 is a radical that can be converted into R_1, converting Z_1 into R_1; or

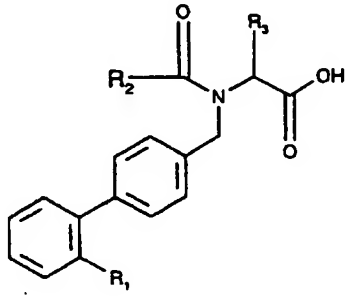
(b) reacting a compound of the formula R_2-COOH (IIIa), a reactive derivative thereof or a salt thereof with a compound of formula (IIIb)



(IIIb)

or a salt thereof; or

(c) reacting a compound of formula (IVa)



(IVa),

a reactive derivative thereof or a salt thereof with a compound of the formula Z_2-C(R_5)(R_6)-OOC-R_4 (IVb), wherein Z_2 is reactive esterified hydroxy, for example in the presence of a base;

and, if desired, converting a compound (I) obtainable according to the process or by other means, in free form or in the form of a salt, into a different compound (I), separating a mixture of isomers obtainable according to the process and isolating the desired isomer, and/or converting a free compound (I) obtainable according to the process into a salt or converting a salt of a compound (I) obtainable according to the process into the free compound (I) or into a different salt.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 97/00493

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D257/04 A61K31/41 C07C233/47 A61K31/165

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 443 983 A (CIBA-GEIGY A.-G., SWITZ.) 28 August 1991 cited in the application see claims ---	1-9
A	FR 2 677 016 A (LABORATOIRES UPSA S. A., FR.) 4 December 1992 see claims --- -/--	1-9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
23 April 1997	02.05.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Sánchez García, J.M.

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INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 97/00493

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 123, no. 17, 23 October 1995 Columbus, Ohio, US; abstract no. 228915, NAKA, YOICHI ET AL: "Preparation of biphenylyltetrazole-containing amino acid and dipeptide derivatives as angiotensin II antagonists" XP002030048 see abstract & JP 07 048 360 A (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD., JAPAN) ---	1-9
A	US 5 260 325 A (MARKWALDER, JAY A. ET AL) 9 November 1993 see claims ---	1-9
A	EP 0 648 763 A (ROUSSEL UCLAF) 19 April 1995 see claims -----	1-9

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